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(54) Title: NOVEL COMPOSITIONS

(57) Abstract

Novel compositions comprising glyceryl monolinoleate are disclosed. Such compositions find utility in the treatment of skin conditions associated with abnormal skin Keratinisation, for example winter xerosis. The composition advantageously contains an antioxidant, and a UV B absorber or reflector.

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NOVEL COMPOSITIONS

The present invention relates to a cosmetic/pharmaceutical product and in particular to a composition for the treatment of conditions associated with abnormal skin keratinisation; a process for the preparation thereof and methods for using the same. In addition, the invention provides a composition which aids in the prevention and treatment of aged appearance, resulting from the detrimental effects of time and environmental damage to the skin.

Skin conditions which are characterised by abnormal keratinisation may include winter xerosis, dry skin, dandruff, seborrheic dermatitis, parakeratosis ichthyoses, psoriasis and acne. The perceived ageing effects of the skin are caused by non-specific oxidative damage to dermal and epidermal cell membranes, such as caused by free radicals generated during normal metabolism, or by ultra violet light (UV) or environmental pollution.

In the present invention we have found that glyceryl monolinoleate compositions are capable of providing an improved skin texture and appearance, and treating the above conditions.

Accordingly there is provided a pharmaceutical or cosmetic composition comprising glyceryl monolinoleate in a suitable carrier. Such carriers will be pharmaceutically and/or cosmetically acceptable.

The invention further provides a composition as described herein for the protection of endogenous essential fatty acids in the skin from oxidation, and the incorporation of linoleate residues (from glyceryl monolinoleate) to replenish any fatty acid residues in the skin cell membrane, which may have been oxidised.

Accordingly the invention provides a composition for treating abnormal keratinisation of the skin.

The composition is also useful for treating and preventing the aged appearance of skin.

Glyceryl monolinoleate has been shown by the present inventors, to possess excellent skin penetration. The rate of penetration of the stratum corneum and viable epidermis is superior to the common sources of linoleic acids and triglyceride oils. The latter are typified by sunflower seed oil, safflower seed oil and evening primrose oil.

The glyceryl monolinoleate is typically present in the range of 0.01 to 25%, preferably 0.05 to 20% by weight of the composition. Most preferably in the range 2.5 to 10% by weight of the composition.

Glyceryl monolinoleate and also linoleate residues occurring naturally within the skin cell membranes can be oxidised, relatively easily, by solar radiation, environmental pollutants and by reactive oxygen species (including hydroxyl free radicals) of the skin. Solar radiation, reaching the earth's surface, in the range 280-320nm (UV-B) induces linoleate free radicals which in turn can react with molecular oxygen and generate further radical production. Unless controlled, this process can result not only in the loss of essential fatty acid from the skin membrane, but also in the generation of organic peroxides which can damage the skin.

The present inventors have found that substances which absorb or reflect UV-B radiation will protect glyceryl monolinoleate and linoleic acid derivatives from UV induced oxidation within the skin.

Accordingly, in a preferred embodiment one or more UV B absorbing and/or reflecting materials are included in the composition which will protect the glyceryl monolinoleate from oxidation.

The UV absorbing material will absorb ultraviolet light in the range 280 - 320 nm.

Examples of UV-reflecting materials include titanium dioxide, zinc oxide and synthetic polymers which are opaque to UV-B light. Such materials should be incorporated into the composition as particles which fall into the size range 0.02 - 20 microns, as measured in the longest dimension. Preferably the size range is 1 - 5 microns.

Examples of UV absorbing materials include octyl methoxycinnamate and octyl dimethyl-p-aminobenzoic acid. Preferably the material is octyl methoxycinnamate.

Suitably the UV-absorbing material is incorporated into the final product such that a film of 25 microns thick yields a sun protection factor (SPF) of 2 or more as determined by the method specified by the Federal Drug Administration, Department of Health, Education, and Welfare (Federal Register Vol 43 No. 166 25th August 78).

The lifetime and efficacy of glyceryl monolinoleate applied to the skin can be significantly enhanced by the addition of an antioxidant or mixture of antioxidants capable of scavenging alkyl peroxide free radicals and/or oxygen free radicals, especially the hydroxyl free radical.

Accordingly, there is provided a composition comprising glyceryl monolinoleate, a UV absorbing material, an antioxidant in a suitable carrier.

Suitable examples of antioxidant materials (alkyl peroxide scavengers) include alpha tocopherol, alpha tocopheryl acetate, propyl gallate, octyl gallate, dodecyl gallate, uric acid and ascorbyl palmitate. Hydroxyl radical scavangers include glycerol, lactic acid and lactic acid salts.

Preferably the composition comprises both an alkyl peroxide free radical scavanger and an hydroxyl free radical scavenger. Preferably these are propyl gallate and glycerol respectively.

The antioxidant component is typically present in the range of 0.01 - 20%, preferably 0.2 - 10% by weight of the composition.

A UV-absorbing material active in the region of 320 nm - 400 nm may also be included in the composition if required. Such material is known as a UV-A absorbing material.

In addition and if necessary, further additives conventionally used in cosmetic compositions, such as humectants, emollients, perfumes, dyes, preservatives and viscosity modifiers may be added.

The composition may be prepared as an oil-in-water or a water-in-oil emulsion, a microemulsion, aqueous ethanolic or other alkanol based gel or lotion. The active ingredient may either totally or partially be encapsulated by liposomes, liposomes-like carriers, or by natural or synthetic polymers.

In this context the term 'oil' refers to emollient materials such as mineral oils, silicones, substituted silicones and alkyl or aryl esters.

Suitably the composition is applied directly to the skin. Treatment may be repeated as required.

The invention further provides a process for the preparation of a composition according to the invention, which process involves admixing the ingredients in a conventional manner.

The invention still further provides a method for the treatment or prevention of a condition associated with excess skin keratinisation, which method comprises the application to the skin of an effective amount of a composition according to the invention.

In an embodiment of the invention, there is provided a method for the prevention, and/or reversion of time and environmental damage to the skin which method comprises the repeated administration to the skin of an effective amount of a composition according to the invention.

The following Examples illustrate the invention.

Example 1

1. Oil-in water cream for the treatment of parakeratotic skin conditions

INGREDIENT	PERCENT w/w
Glyceryl Monolinoleate	5.00
Octyl Dimethyl-p-Amino-Benzoic Acid	6.00
Alpha Tocopheryl Acetate	5.00
Butylated Hydroxytoluene	0.03
Mineral Oil	18.00
Cetyl Alcohol	2.00
Dimethyl Polysiloxane	1.00
Nipastat	0.30
Nipabutyl	0.02
Stearic Acid	3.00
Imidazolidinyl Urea	1.80
Triethanolamine	1.20
Carbomer 941	0.20
Deionised Water	56.45

Example 2

2.Water-in-oil cream for protection of the skin against environmentally induced accelerated ageing

INGREDIENT	PERCENT w/w
Glyceryl Monolinoleate	5.00
Octyl Methoxycinnamate	6.00
Alpha Tocopherol	2.00
Butyl Methoxydibenzoylmethane	2.00
Mineral Oil	18.00
Ceresin Wax	2.00
Polyethylene Glycol/ Dodecyl Glycol Copolymers	2.00
Nipastat	0.30
Nipabutyl	0.02
Stearic Acid	3.00
Imidazolidinyl Urea	1.80
Glycerol	10.00
Deionised Water	47.88

Example 3

Ethanolic gel for the treatment of acne

INGREDIENT	PERCENT w/w
Glyceryl Monolinoleate	1.00
Octyl Methoxycinnamic Acid	6.00
Uric Acid	1.00
Ethanol	30.00
Carbomer 940	1.00
Nipastat	0.30
Nipabutyl	0.02
Triethanolamine	0.25
Deionised Water	60.43

Example 4

4. Hair lotion for the treatment of dandruff

INGREDIENT	PERCENT w/w
Glyceryl Monolinoleate	1.00
Ethyl Dimethyl-p-amino-Benzoic Acid	2.00
Glycerol	1.00
Ethanol	40.00
Carbomer 940	0.10
Nipastat	0.30
Nipabutyl	0.02
Triethanolamine	0.03
Deionised Water	55.55

Example 5

(1) Skin Cream Formulation

INGREDIENT	PERCENT w/w
Germaben II (Anti-Microbial)	1.00
Polawax GP 200 (Emulsifier, Polyethyne Glycol Stearate and Wax)	1.25
Nipanox S-1 (Anti-Oxidant, Propyl Gallate)	0.01
Glyceryl Monolinoleate	5.00
Octyl Palmitate (Emollient)	2.00
Parsol 1789 (UVA-Absorber)	0.50
Sorbithom SE-C (Emulsifier, Sorbitain Stearate)	1.50
Sorbithom Tep (Emulsifier)	2.00
Lexemul 561 (Emusifier, Glyceryl Monostearate)	3.00
Cetyl Alcohol (Emollient Emulsifier, Wax)	3.50
Dimethicone 350 (Anti-foam, Dimethyl Polysiloxane)	1.00
Octyl Methoxycinnamate (UVB Absosrber)	2.00
Acumist B-6 (Solid Lubricant, Polyethylene Microspheres)	2.00
Alpha Bisabolol (Anti-Irritant)	0.06
Glycerol (Free Radical Scavenger and Humectant)	5.00
Triethanolamine (Neutralising Agent for Carbopol 981)	0.14
Carbopol 981 (Polyacrylate Polymeric Thickener)	0.10
Florenthys 37.423 (Perfume)	0.20
Deionised Water	69.74
	100.00

Example 6

(1) Skin Cream Formulation

INGREDIENT	PERCENT w/w
Germaben II (Anti-Microbial)	1.00
Polawax GP 200 (Emulsifier, Polyethyne Glycol Stearate and Wax)	1.25
Nipanox S-1 (Anti-Oxidant, Propyl Gallate)	0.01
Glyceryl Monolinoleate	5.00
Alpha Tocopherol (Free Radical Scavenger)	1.50
Octyl Palmitate (Emollient)	2.00
Parsol 1789 (UVA-Absorber)	0.50
Sorbithom SE-C (Emulsifier, Sorbitain Stearate)	1.50
Sorbithom Tep (Emulsifier)	2.00
Lexemul 561 (Emusifier, Glyceryl Monostearate)	3.00
Cetyl Alcohol (Emollient Emulsifier, Wax)	2.00
Dimethicone 350 (Anti-foam, Dimethyl Polysiloxane)	1.00
Octyl Methoxycinnamate (UVB Absosrber)	2.00
Acumist B-6 (Solid Lubricant, Polyethylene Microspheres)	2.00
Alpha Bisabolol (Anti-Irritant)	0.06
Glycerol (Free Radical Scavenger and Humectant)	5.00
Triethanolamine (Neutralising Agent for Carbopol 981)	0.14
Carbopol 981 (Polyacrylate Polymeric Thickener)	0.10
Florenthys 37.423 (Perfume)	0.20
Deionised Water	69.74
	100.00

Example 7(a)

GML Test Cream

INGREDIENT	PERCENT w/w
Glyceryl Monolinoleate	5.00
Mineral Oil	11.00
Stearic Acid	2.00
Cetyl alcohol	3.50
Nipabutyl Anti-Microbial	0.02
Nipastat Anti-Microbial	0.30
Germall 115 Anti-Microbial	0.30
Nipanox Special Anti-Oxidant	0.01
Triethanolamine	0.80
Distilled Water	77.07
	100.00

Example 7(b)

Control Cream

INGREDIENT	PER CENT w/w
Mineral Oil	11.00
Stearic Acid	2.00
Cetyl Alcohol	3.50
Nipabutyl Anti-microbial	0.02
Nipastat Anti-Microbial	0.30
Germall 115 Anti-microbial	0.30
Nipanox Special Anti-oxidant	0.01
Triethanolamine	0.80
Distilled Water	82.07
	100.00

Example 8

Clinical Efficacy of Glyceryl Monolinoleate - Parakeratosis

A double blind trial of the clinical efficacy of Glyceryl Monolinoleate (GML) was carried out in which 16 subjects used a cream containing 5% GML (Example 7a) and 19 subjects used a similar cream (Example 7b) which did not contain GML. The treatment period lasted 8 weeks.

Immediately before the start of the treatment period and immediately on cessation of the treatment period, the degree of parakeratosis of the volunteers' facial skin was determined. This was achieved by removing a sample of the outermost cell-layer of the stratum corneum with adhesive tape, staining with haematoxylin/eosin and counting the cell-nuclei per unit area.

Under the (winter) conditions in which the group using the control cream underwent a significant mean increase in the degree of facial skin-parakeratosis, the group using the GML-containing cream showed no such increase. This difference in response to topical treatment with the two creams was statistically significant ($p=0.05$).

Such a result indicates a beneficial effect of GML on the nature of epidermal differenciation, being manifested during environmental stress as a protective effect.

Hence, the effect of GML was tested in respect of its effect on facial skin appearance, given that improved or protected epidermal differenciation is a key factor in improving or retaining the appearance of the skin when this is placed under environmental stress.

Example 9(a)

Control Cream

INGREDIENT	PERCENT w/w
Octyl Palmitate	7.00
Arlacel 60	1.50
Tween 60	2.00
Arlacel 165	5.00
Cetyl alcohol	3.50
Dimethicone 350	1.00
Nipastat	0.30
Nipabutyl	0.02
Nipanox Special	0.01
Germall 2	0.30
Triethanolamine	0.17
Carbopol 941	0.10
De-Ionised Water	79.10

Example 9(b)

GML Test Cream

INGREDIENT	PERCENT w/w
Octyl Palmitate	2.00
Glyceryl Monolinoleate	5.00
Arlacel 60	1.50
Tween 60	2.00
Arlacel 165	5.00
Cetyl alcohol	3.50
Dimethicone 350	1.00
Nipastat	0.30
Nipabutyl	0.02
Nipanox Special	0.01
Germall 2	0.30
Triethanolamine	0.17
Carbopol 941	0.10
De-Ionised Water	79.10

Example 9(c)

Enhanced GML Test Cream

INGREDIENT	PERCENT w/w
Octyl Palmitate	2.00
Glyceryl Monolinoleate	5.00
Arlacel 60	1.50
Tween 60	2.00
Arlacel 165	5.00
Cetyl alcohol	3.50
Dimethicone 350	1.00
Nipastat	0.30
Nipabutyl	0.02
Nipanox Special	0.01
Germall 2	0.30
Triethanolamine	0.17
Carbopol 941	0.10
Parsol 1789	1.00
Parsol MCX	4.00
Acumist B6	2.00
Bisabolol. Synthetic	0.10
Glycerol. 98% minimum	10.00
Soluble Collagen	0.10
De-Ionised Water	61.90

Example 10

GML treatment of Winter Xerosis

A double blind trial of the clinical efficacy of Glyceryl Monolinoleate was carried out by an independent research organisation (HillTop Research Inc., Winnipeg Branch, 200-584 Pembina Highway, Winnipeg, Manitoba, Canada).

Glyceryl Monolinoleate (GML) in an oil-in-water emulsion, termed "GML Cream" (Example 9b), was compared with the emulsion itself, the Control Cream (Example 9a), in respect of their efficacy in reducing or eliminating facial Winter Xerosis (winter "dry" flaking skin). In the same trial, these two emulsions were compared with a similar emulsion containing GML together with a UVB-absorber and a scavenger of hydroxyl free radicals. This emulsion is termed "Enhanced GML Cream (Example 9c)". The latter contained octyl methoxy cinnamate as UVB-absorber and contained glycerol as a hydroxyl radical scavenger.

The trial was began with a standardisation phase of one week during which all the female volunteers used the control emulsion.

Thereafter, 75 volunteers entered the 8-week treatment phase of the trial. During the treatment phase, 25 volunteers began using the Control Cream, 25 volunteers began using the GML Cream and 25 volunteers began using the Enhanced GML Cream.

Prior to entering the treatment phase and every 2 weeks during this phase, the volunteers' facial skin condition was monitored and recorded by a trained observer.

The 8-week treatment phase was followed by a 2-week "regression" phase during which all of the volunteers in the trial used the Control Cream. Facial skin condition was monitored in the subsequent 3 days, 7 days and 14 days of the regression period.

Immediately before the start of the treatment period and immediately on cessation of the treatment period, the degree of parakeratosis of the volunteers' facial skin was determined. This was achieved by removing a sample of the outermost cell-layer of the stratum corneum with adhesive tape, staining with haematoxylin/eosin and counting the cell-nuclei per unit area.

Of the 26 volunteers who began the treatment phase using the GML Cream, 23 completed it. Of the 25 volunteers who began the treatment phase using the Control Cream, 23 completed it. Of the 24 volunteers who began the treatment phase using the Enhanced GML Cream, 23 completed this phase.

The trial demonstrated the ability of both the GML Cream and the Enhanced GML Cream to reduce facial flaking skin as compared with the Control Cream. All through the treatment phase, the performance of both the GML Cream and the Enhanced GML Cream was superior to the Control Cream.

In respect of the severity of the volunteers' flaking facial skin, the superiority of the GML Cream was statistically significant at the 2-week ($p<0.01$) and 4-week ($p<0.02$) stages of treatment.

In respect of the severity of the volunteers' flaking facial skin, the superiority of the Enhanced GML Cream was statistically significant at the 2-week ($p<0.02$), 4-week ($p<0.001$), 6-week ($p<0.02$) stages of treatment.

After 3 days into the regression phase, the superior performance of both the GML Cream and the Enhanced GML Cream was maintained over the Control Cream although the differences from the latter were reduced compared with the treatment phase. The superiority of the Enhanced GML Cream was statistically significant at this 3-day time point ($p<0.03$). Thereafter, during the regression phase, no significant differences were detectable when either of the GML Creams was compared with Control Cream.

Facial fine lines were significantly reduced in the group using the GML Cream compared with the group using the Control Cream at the 6-week time point of the treatment period ($p=0.05$).

The group using the Enhanced GML Cream underwent significant reductions in facial fine lines compared with the groups using the GML Cream or the Control Cream at the 2-week ($p=0.01$) and 4-week ($p=0.02$) time points of the treatment period.

Between the start and end of the treatment period, users of both the GML Cream and the Enhanced GML Cream underwent statistically significant reductions in skin parakeratosis, as judged by the numbers of cell-nuclei migrating to the skin surface. However these changes were not statistically significant from those undergone by users of the Control Cream, who also underwent a significant reduction in parakertosis. The latter lack of detectable significant difference is attributable to a marked improvement in the environmental temperature during the latter stages of the trial.

Hence the results confirmed the hypothosis that topical application of GML would cause a significant reduction in "dry" flaking facial skin as compared with a bland control cream.

Similarly, the hypothesis that this efficacy would be enhanced by the co-administration of a UVB-absorber and a UVB-absorber and a scavenger of hydroxyl free radicals was confirmed.

Claims

1. A pharmaceutical or cosmetic composition comprising glyceryl monolinoleate in suitable carrier.

2. A pharmaceutical or cosmetic composition as claimed in claim 1 additionally comprising one or more UV B absorbing or reflecting material.

3. A pharmaceutical or cosmetic composition as claimed in claim 2 wherein a UV B reflecting material is selected from titanium dioxide or zinc oxide.

4. A pharmaceutical or cosmetic composition as claimed in any one of claims 1 to 3 which additionally comprises an antioxidant.

5. A pharmaceutical or cosmetic composition as claimed in claim 4 wherein the antioxidant component comprises both an alkyl peroxide free radical scavenger and an hydroxyl free radical scavenger.

6. A pharmaceutical or cosmetic composition as claimed in any of claims 1 to 5 additionally comprising a UV A absorbing material.

7. A composition as claimed in any of claims 1 to 6 for use in medicine.

8. A composition as claimed in any of claims 1 to 6 for cosmetically treating the appearance of the skin.

9. A composition as claimed in any of claims 1 to 6 for treating and preventing the aged appearance of the skin.

10. Use of glyceryl monolinoleate in the manufacture of a medicament for treating abnormal Keratinisation of the skin.

11. Use of glyceryl monolinoleate in the manufacture of a medicament for treating any of winter xerosis, dry skin, dandruff, seborrheic dermatitis, parakeratosis icthyoses, psoriasis, and acne.

12. A method for the treatment or prevention of a condition associated with excess skin Keratinisation, which method comprises the application to the skin of an effective amount of a composition according to any of claims 1 to 6.

13. A method for the prevention and/or reversion of time and environmental damage to the skin which method comprises the repeated administration to the skin of an effective amount of a composition according to any of claims 1 to 6.

14. A process for the production of a composition as claimed in any of claims 1 to 6, the process comprising admixing glyceryl monolinoleate with an acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/02211

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 7/48 A 61 K 7/42 A 61 K 31/23

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K 7/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0103910 (THE PROCTER & GAMBLE CO.) 28 March 1984, see claims; page 5, lines 31-33; page 16, lines 24-32; page 19, lines 4-8 ---	1-3,7-9 ,11,14
A	US,A,3957969 (Y. FUJIYAMA et al.) 18 May 1976, see claims; column 2, lines 47-60; column 3, lines 55-66, example 1 ---	1-6,8, 14
A	US,A,4025645 (C. JELENKO) 24 May 1977, see abstract; claims ---	1,4,5,7 ,10,11
A	H. JANYSTIN: "Taschenbuch der modernen Parfümerie und Kosmetik", published 1966, Wissenschaftliche verlagsgesellschaft mbH, Stuttgart, DE, see pages 264,265 -----	1

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13-03-1992	10 APR 1992
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: MISS I. TAZELAAR

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 12, 13 because they relate to subject matter not required to be searched by this Authority, namely:
(Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods)
Rule 39.1 (iv) PCT

2. [ ] Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9102211 SA 54419

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0103910	28-03-84	None	
US-A- 3957969	18-05-76	None	
US-A- 4025645	24-05-77	None	